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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/560,157	PIETRANGELO, ANTONELLO	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *7/8/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *5-10 and 22-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,11-21 and 50-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/05; 10/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed July 8, 2008. Currently, claims 1-52 are pending. Claims 5-10, 22-49 have been withdrawn as drawn to non-elected subject matter.

Election/Restrictions

2. Applicant's election with traverse of Group I, Claims 1-4, 11-21, 50-52 in the paper filed July 8, 2008 is acknowledged.

The response asserts that there would be no burden to search Groups I-III together, citing 803. The response asserts that each mutation comprises a single nucleotide substitution of SEQ ID NO: 2 and is associated with non-HFE hemochromatosis. This argument has been reviewed but is not persuasive. This application was filed under 371 and considers whether there is a single inventive concept which links the inventions. Here, as noted in the initial lack of unity requirement, claims drawn to 10 nucleotides do not make a contribution over the art. Furthermore, Group I, II and III are directed to mutations in the ferroportin 1 gene. Mutations within the ferroportin 1 gene were known in the art at the time the invention was made, including A77D. Thus, there is no special technical feature which links the inventions and Groups I, II, and III will not be rejoined.

Claims 5-10, 22-49 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or

linking claim. Applicant timely traversed the restriction (election) requirement in the paper filed July 8, 2008.

The requirement is still deemed proper and is therefore made FINAL.

This application contains Claims 5-10, 22-49 drawn to an invention nonelected with traverse in the paper filed July 8, 2008. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Priority

3. This application is a 371 of PCT/EP04/51068, filed June 9, 2004. The application also claims priority to ILALY MI2003A001156, filed June 9, 2003.

It is noted that a translation of the foreign document has not been received.

Drawings

4. The drawings are objected to. The drawings are hard to read and illegible in some places. For example, Figure 1A appears to have numbers or letters in the figure, but they are illegible. The Figure 1B also appears to have letters or numbers which are illegible. Appropriate correction is required.

Claim Objections

5. Claims 16 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is

required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

It appears that Claim 16 is directed to a polynucleotide comprising SEQ ID NO: 9-27. However, Claim 16 is dependent on Claim 15. Claim 15 requires that the polynucleotide comprise at least one polymorphic nucleotides corresponding to potion 238 of SEQ ID NO: 3. SEQ ID NO: 9 is directed to exon 1. SEQ ID NO: 9 does not overlap with position 238 of SEQ ID NO: 3 which is in exon 3. Appropriate correction is required. SEQ ID NO: 13-14 are taught to amplify exon 3, but they amplify the whole coding region and do not overlap with the polymorphism.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

6. Claims 15-17 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The instant claims are directed to polynucleotides. The claims are not directed to an isolated polynucleotide molecule such that the claims would be directed to statutory subject matter. This rejection may be easily overcome by amending the claims to recite an "isolated polynucleotide" such that it is clear that the "hand of man" is required and the product is nonnaturally occurring.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4, 11-14, 18-21, 50-51 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to isolated polynucleotides coding for a ferroportin mutated at position 80 of SEQ ID NO: 2 compared to the wild type sequence. The specification teaches three species within the claimed genus: specifically the protein having an amino acid at position 80, 174 or 248 altered.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2b 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed". Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. In *The Regents of the University of California v. Eli Lilly* (43 USPQ2b 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to

disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...' required a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

In analyzing whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. As provided in the written description guidelines, Example 10, the three species, namely mutation at position 80, 174, 248 of SEQ ID NO: 2 coding for a ferroportin 1 mutated gene does not provide description for the full scope. There is substantial variability among the species of DNAs encompassed within the scope of the claims. The claimed isolated polynucleotides can vary significantly in structure and there is no teaching in the specification regarding which amino acid positions are required to retain the function as a ferroportin 1. There is no art-recognized correlation between any structure (other than the 3 mutations provided) and the activity of a ferroportin 1 mutated protein that those of ordinary skill in the art could predict which isolated polynucleotides code for a ferroportin 1 mutated protein. One skilled in the art would not recognize from the disclosure that the applicant was in possession of the genus of isolated polynucleotides coding for a ferroportin 1 mutated at position 80 of SEQ ID NO: 2, compared to the wild type. There is no information about which amino acids can vary from "the wild type" in the claimed genus of coding sequences and still

retain the ferroportin 1 activity. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus. Accordingly, Applicants have not adequately disclosed the relevant identifying characteristics of a representative number of species within the claimed genus.

Claim Rejections - 35 USC § 112-Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1-4, 11-21, 50-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the

relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-4, 11-21, 50-52 are drawn to polynucleotide coding for a ferroportin 1 mutated at position 80 of SEQ ID NO: 2 compared to the wild type sequence.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches the ferroportin 1 gene and mutations at A77D in exon 3.

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent

research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Guidance in the Specification.

The specification provides no evidence that the G80S mutation in the ferroportin 1 gene is associated with impaired ion homeostasis or hereditary hemochromatosis. The specification states that the G80S mutation is found, however fails to provide any information as to whether the mutation is indicative of a disease in a reliable significant manner. The specification does not teach how to use the C or T variant in the nucleic acid.

The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied to enable the skilled artisan to use the claimed invention as broadly as claimed.

The specification does not teach whether the G80S polymorphism is found in normal individuals or whether the mutation is found only in affected patients. If the mutation is found in both normal and affected patients, then it is unclear how the skilled artisan would use the polynucleotide. A polynucleotide to the mutant allele does not appear to have any use unless the skilled artisan could assess the disease state of an individual. Moreover, the specification does not teach how to use the C or T variant in the nucleic acid. Neither the art, nor the specification teaches whether the C or T variant is present in the population and then how the skilled artisan could use an isolated polynucleotide comprising a C or T.

This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where associations of polymorphisms with traits is unpredictable and the prior art and the specification fail to provide robust association studies, the guidance is insufficient

guidance to overcome the art recognized problems of association studies. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112- Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-4, 11-21, 50-52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claims 1-4, 50-51 are indefinite over the recitation "isolated polynucleotides..." because it is unclear whether multiple copies of the same polynucleotide are required or whether the claim requires several different polynucleotides that encode ferroportin 1 and are mutated at position 80 of SEQ ID NO: 2 compared to the wild type.

B) Claims 1-4, 50-51 are indefinite over the recitation "the wild type sequence" because "the wild-type sequence lacks proper antecedent basis." Moreover, it is

unclear whether the claims require "the wild-type" sequence except have only one change at position 80 of SEQ ID NO: 2 or whether the sequence may have many mutations with respect to the wild-type sequence.

C) Claims 2-4, 11-21, 52 use the transition phrase "characterized in" and "characterized by". It is unclear whether the language is open or closed transitional language and what is encompassed by the claim. For example, in Claim 3 it is unclear whether the claim requires a polynucleotide comprising SEQ ID NO: 1 with a polymorphism at 238. Clarification is required.

D) Claims 14-17, 52 are indefinite over the recitation "corresponds to ..." because it is unclear what the transition corresponds to encompasses. Correspondence is not an art recognized term for identify, homology or equivalence. It is unclear what it means that the sequence corresponds to SEQ ID NO: 3. The specification fails to provide any definition for corresponds. Thus, the metes and bounds of the claimed invention are unclear.

E) Claim 15-17 are indefinite over the recitation "derived from" because this language does not particularly set forth whether the polynucleotides are limited to fragments of the SEQ ID NO: 3 overlapping position 238 or can include sequences which were originally taken from SEQ ID NO: 3 but are then modified in sequence, i.e. by additions, deletions, substitutions, such that the polynucleotide sequences are not the same as given in SEQ ID NO: 3.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 15, 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Fodor (US Publication 2001/0053519, December 20, 2001).

Fodor teaches analysis using a 10-mer array (Example 2, col. 22). Figures 2-5 show results from the hybridization of a sample of DNA to an array containing all possible 10-mers which was manufactured using photolithography techniques on an array. Therefore, Fodor teaches a polynucleotide carrying at least 10, namely 10, consecutive nucleotides from SEQ ID NO: 3 and characterized by comprising at least one of polymorphic nucleotides corresponding to position 238 of SEQ ID NO: 3.

Since Fodor teaches every 10-mer, Fodor inherently teaches a polynucleotide as claimed.

Conclusion

11. No claims allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine Goldberg/
Primary Examiner
October 28, 2008